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### STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Thoureen (author), Dr. Scott (author), Dr. Best (author), Dr. LoVecchio (peer reviewer), Dr. Wise (editor), Ms. Coplin (executive editor), and Ms. Hamlin (managing editor) report no financial relationships relevant to this field of study.

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# Urinary Tract Infection

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## Definition of the Problem

Urinary tract infections (UTIs) were the most common bacterial infection encountered in ambulatory settings in 2007[1] and the most common primary diagnosis for women visiting the emergency department.[2] One in three women will develop a UTI requiring antibiotics by age 24, and half of all women experience at least one UTI in their lifetime.[3] More than 8 million medical visits per year are for the chief complaint of UTI and the diagnosis accounts for 100,000 admissions annually.

It's common to divide urinary tract infections into upper or lower UTI, based on the anatomic location of the infection. Cystitis is an infection of the bladder and considered to be lower tract. Pyelonephritis and pyelitis are considered infections of the upper tract, but may also include the lower tract.

Urinary tract infections may be further classified as uncomplicated or complicated. This classification is based on patient comorbidities and the presence of anatomic or physiologic abnormalities that predispose to UTI. Uncomplicated UTIs are episodes of cystitis or pyelonephritis in premenopausal, non-pregnant women without structural or functional urinary tract abnormalities. Complicated UTIs occur in patients with abnormal urinary anatomy or significant medical or surgical comorbidities.[4] (*See Table 1.*) Patients with complicated UTIs typically need prolonged courses of antibiotics and interventions.

Asymptomatic bacteriuria is another entity defined by a clean catch urine specimen that grows $10^5$ CFU/mL of the same uropathogen (no more than two) in a patient who has no symptoms and has not had a urinary catheter in the seven days preceding the urine culture.[5,6] Females require two consecutive samples that are positive for growth and males just one.

## Epidemiology

UTI is much more common in women than in men. Of the more than 3 million visits for UTI in 2010, 84.5% were women. The incidence of UTI in this group was highest from the end of the second decade of life through the fifth decade.[7,8] Overall, women also have a higher rate of pyelonephritis than men, with the greatest peak at age 15-35 years old. As adults, men have a gradual rise in the incidence of pyelonephritis after age 35, with incidence peaking at 85 years old.[9]

## EXECUTIVE SUMMARY

- Dysuria, frequency, and urgency in a young healthy woman without vaginal irritation is sufficient to diagnose a UTI and initiate antibiotic treatment.
- A positive urinary dipstick for nitrite and leukocyte esterase (moderate or large) is highly predictive of a UTI.
- Urine cultures are indicated in complicated UTIs and in treatment failures when a second antibiotic course is being initiated.
- Nitrofurantoin is the recommended antibiotic for initial treatment of an uncomplicated UTI.
- Fluoroquinolones are the first-line therapy for the outpatient management of acute pyelonephritis.

## Etiology

*Escherichia coli* has been known for many years to be the most common causative bacteria in UTIs. This is true for uncomplicated and complicated UTI and for lower and upper UTI. *Staphylococcus saprophyticus* causes 5-15% of UTI in young females. The remaining infections are caused by Proteus, Klebsiella, Enterococcus, and group B Streptococcus.[10] Klebsiella and Enterobacter are seen particularly in patients older than 55 years.[9] Complicated and catheter-associated UTIs have a much greater variety of causative organisms, including: polymicrobial, extended-spectrum beta-lactamase (ESBL) producing organisms, Pseudomonas, and *Enterococcus faecium*.

## Prediposing Factors

**Gender.** As stated previously, females are overwhelmingly more affected by UTI than males. This is likely due to anatomic differences in the length of the urethra. It is believed that the shorter length urethra in females facilitates bacterial transit to the bladder. Other risk factors for UTIs in females include past history, family history, hormonal levels, and sexual practice. (*See Table 2.*)

**Elderly.** The elderly are a particularly challenging population that develops UTIs. Asymptomatic bacteriuria (ASB) is very common in the elderly. The incidence of ASB in individuals older than 65 years living at home is about 10% in men and 30% in women, compared with those residing in long-term care facilities at 15-40% in men and 55% in women.[11-15] In general, patients with ASB do not require antibiotics, but it adds to the difficulty in diagnosis and potentially overtreatment with antibiotics in the elderly. Treatment of ASB is not associated with an effect on mortality or a reduction in symptomatic UTIs.[13,16] Other challenges in this population include a blunted fever response[17] and more atypical symptoms of UTI in institutionalized patients, for example change in mental status, weakness, lethargy, and abdominal pain.[18,19] *E. coli* is still the most prominent bacteria identified, but an increased percent of Proteus, Klebsiella, Enterococcus, and Pseudomonas are identified compared to the same cohort younger than 65 years old.[20]

**Diabetes.** Patients with diabetes have a higher frequency of UTIs, and given their comorbid illness, these UTIs are considered to be complicated. The most important factors influencing the development of a UTI in diabetics specifically are the duration of diabetes and presence of long-term complications of diabetes, such as neuropathy.[21] Diabetes is also associated with more severe presentations of UTI, such as perinephric abscess.[22]

**Immunocompromised Patients.** The most common infection in renal transplant patients is UTI.[23,24] The risk of infection is the highest in the first year after transplant.[25] There are several factors that may increase risk in this patient population. (*See Table 3.*)

Patients with HIV certainly should be considered among an immunocompromised population; however, there has not been any directly attributable factors consistently identified to show an increased incidence simply because of HIV infection.[26] Male patients with HIV may have a higher risk for prostatitis, but other factors, such as direct correlations of CD4 counts, have not been found to be consistently helpful.

**Spinal Cord Injuries.** UTIs and renal failure used to be the most common cause of death in patients with spinal cord injury until the introduction of the current recommendations for bladder management. These consist of intermittent catheterization, condom catheters, sphincterotomy, and surgical procedures such as ileal conduit, cystoplasty, and other urinary diversions for select patients.[27] The increased risk of UTI in patients with spinal cord injury is due to the impaired bladder emptying that is associated

### Table 1. Factors Indicating a Complicated UTI[4]

- Indwelling catheters
- Obstruction
- Male gender
- Age
- Diabetes mellitus
- Renal insufficiency
- Immunosuppression
- Urolithiasis
- Surgery
- Voiding dysfunction
- Ureteral valves
- Vesicoureteral reflux
- Pregnancy
- Nosocomial

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**Table 2. Risk Factors for UTI in Females[1,3,88-90]**

- Prior history of UTI
- Vaginal intercourse in last 2 weeks
- Use of contraception with spermicide
- New sexual partner (in past year)
- Low vaginal estrogen levels
- History of UTI in first-degree relative

with a neurogenic bladder. The risk of UTI in patients with spinal cord injury is similar for men and women. UTI is the most frequent cause of rehospitalization in the first year after traumatic spinal cord injury.[25] Risks for symptomatic infection include: age greater than 40 years, hyperreflexic bladder with detrusor-sphincter dysynergy, a cervical level of injury, indwelling catheter, vesicoureteral reflux, and invasive procedure.[25]

**Indwelling Catheters.** Catheter-associated urinary tract infection (CAUTI) refers to a urinary infection in a person whose urinary tract is catheterized or has been catheterized within the previous 48 hours. CAUTI represents up to 40% of all healthcare-associated infections.[28-30] Seventy percent of healthcare-associated UTIs are related to catheters, and 95% of UTIs in intensive care settings are due to catheters.[31] The duration of the catheter is the dominant risk factor for infection.[29,30] Other risk factors for CAUTI include: age greater than 50 years, non-surgical disease, rapidly fatal illnesses, hospitalization on an orthopedic or urologic service, diabetes mellitus, catheter insertion outside of the operating room, and serum creatinine > 2 mg/dL when catheter is inserted.[32]

## Pathophysiology

Uncomplicated UTI is typically caused when pathogens from the bowel or vagina colonize the urethra and ascend to the bladder. If these pathogens continue to ascend further, the ureters and kidneys also become infected. There is a specific uropathogenic subset of *E. coli* that has the potential for enhanced virulence. These virulence adaptations include: fimbriae, flagella, diverse adhesions, siderophores, toxins, and other properties that allow it to avoid or subvert host defenses, set off cascades of immunologic responses, and invade the host cells and tissues.[33,34] Uropathogenic strains of bacteria can persist in fecal flora for years after treatment for the UTI and can cause recurrent infection.[34]

**Table 3. Identified Risk Factors for Increased Frequency of Urinary Tract Infection or Bacteriuria Following Renal Transplant**

| Exposure | Risk Factor |
|---|---|
| Pretransplant | Female<br>Diabetes mellitus<br>Prolonged dialysis<br>Polycystic kidney disease<br>Pretransplant urinary infection |
| Transplant procedure | Deceased donor<br>Allograft trauma<br>Microbial contamination of cadaver kidney<br>Technical complications with anastomosis<br>Indwelling urinary catheter<br>Ureteral stent |
| Posttransplant | Urinary tract obstruction<br>Immunosuppressive therapy<br>Vesicoureteral reflux<br>Reimplantation<br>Acute rejection episodes |

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## Clinical Features

Common presenting symptoms of cystitis are urinary frequency, urgency, dysuria, stranguria (difficulty passing urine; only small drops come when attempted), lower abdominal pain, and/or low back pain. Hematuria, fevers, chills, and malaise may also be reported. In elderly patients or in critically ill patients, symptoms referable to the urethra or bladder are often absent, and instead, presenting features may be nonspecific, including: delirium, urinary retention or incontinence, metabolic acidosis, or respiratory alkalosis. Physical exam findings for cystitis range from a normal physical exam to isolated lower abdominal tenderness.

The clinical presentation for pyelonephritis is classically taught as a patient with a tetrad of high fever, costovertebral angle tenderness, signs or symptoms of lower urinary tract infection, and positive urinary culture. However, in a recent study, the three clinical symptoms together (high fever, costovertebral pain and/or tenderness, signs or history of recent UTI) were present in only about 35% of patients studied. Furthermore, lower urinary tract symptoms were present in fewer than half of the total patients enrolled.[35] Other nonspecific symptoms in pyelonephritis include nausea/vomiting, anorexia, fever/chills, hematuria, upper abdominal pain, general malaise, and weakness. Physical exam findings may include fever, abdominal tenderness to palpation, and/or costovertebral angle tenderness.

## Diagnostics

There are four symptoms (fever, dysuria, frequency, back pain) and one sign (CVA tenderness) that increase the probability of UTI when present to between 60-90%.[36] In young, healthy women, a combination of typical symptoms, in the absence of vaginal irritation or discharge, is sufficiently accurate to initiate antibiotic treatment without further laboratory investigations, yielding a probability of UTI of more than 90%.[37]

**Urine Dipstick and Urine Microscopy.** The urine dipstick is a quick and inexpensive test. A cost analysis study found the cost to perform a urine dipstick was on average $3.05.[38] The data that can be obtained from a urine dipstick include: leukocyte esterase, nitrites, protein, pH, blood, specific gravity, ketones, bilirubin, glucose, and urobilinogen. Although the urine

dipstick is sensitive for detecting leukocyte esterase, blood, and protein, these findings are not specific for infection. The most specific finding for UTI from a urine dipstick is nitrites. The likelihood for disease is highest when leukocytes and nitrites are found on a urine dipstick, with a positive predictive value of approximately 88% when a combination of leukocyte esterase (moderate or large) and nitrites are present.[39] Alternatively, the negative predictive value when blood, leukocyte esterase, and nitrite were absent was 94%.[39]

The urine microanalysis, which typically is performed in a laboratory under a microscope, quantifies the number of white blood cells (WBCs), bacteria, red blood cells (RBCs), organisms and epithelial cells. The urine microanalysis also may contain information on other sediment found in the urine such as crystals and casts. The microscopic urinalysis is highly sensitive for WBCs, and highly specific for UTI if both WBCs and bacteria are present. Conversely, the negative predictive value is also quite high, approaching 93%, if WBC and RBCs are not present on urine microanalysis.[39]

**Urine Culture.** The most common reference standard for the diagnosis of UTI is the presence of $10^5$ colony forming units (CFUs) per milliliter of a single pathogen in a clean catch or catheterized specimen of urine.[36] Historically, urine cultures have proven to be cost ineffective in most patients with a UTI and to rarely change patient outcomes.[40,41] There are conflicting opinions in the literature as to when a urine culture should be obtained. Since a urine culture typically takes three days to result, and some treatment regimens are the same duration, there is literature support for not sending urine cultures on uncomplicated urinary tract infections.[42,43]

Expert opinion supports sending urine culture in four circumstances. The Infectious Disease Society of America recommends urine cultures in patients with pyelonephritis.[32] There is evidence to support sending a urine culture when there has been a clinical treatment failure and a second course of antibiotics is to be initiated.[33-35] In the past decade, resistance to standard antimicrobial therapy for urinary tract infections has increased, especially in patients considered at high risk.[36] Therefore, it is advised to obtain urine cultures for patients diagnosed with complicated UTIs. Urine cultures are also recommended when the patient has severe sepsis or septic shock and a urinary source for the infection is a possibility.

**Blood Culture.** In the uncomplicated UTI, blood cultures are not warranted and have not proven to change the course of treatment for patients with uncomplicated pyelonephritis.[44-46]

## Table 4. Differential Diagnosis

| Disease | Characteristics |
|---|---|
| Cystitis[91] | Dysuria, hematuria, increased urinary frequency, abrupt onset of symptoms, severe symptoms, suprapubic/low back pain or suprapubic tenderness |
| Pelvic Inflammatory Disease[92] | Lower abdominal pain with abnormal vaginal discharge, fever, vomiting, menstrual irregularities, marked tenderness of the pelvic organs on bimanual, and/or palpable adnexal mass |
| Interstitial Cystitis[93] | Abdominal tenderness and intense bladder spasms |
| Vaginitis[94] | Depending on the etiology, can cause vaginal discharge, puritis, pain, and external dysuria (pain as the urine stream flows over inflamed labia) |
| Bladder Cancer[95] | Hematuria, which is typically intermittent, frank, painless, and at times present throughout micturition |
| Urethritis[96] | Urethral discharge, dysuria, pelvic pain |
| Findings Uncommon in UTI and Suggesting Other Infections[91] | Gradual onset, mild symptoms, vaginal discharge/bleeding, lower abdominal pain, new sexual partner, vulvovaginal herpetic lesions on examination, vaginal discharge/odor, pruritus, dyspareunia, external dysuria, and absence of increased frequency or urgency |

## Table 5. Recommended Oral Antibiotics for Acute Uncomplicated Cystitis[64]

| Antibiotic | Example Antibiotic Dosing and Duration |
|---|---|
| 1st Line Treatment | |
| Nitrofurantoin | 100 mg BID × 5 days |
| TMP-SMX** | 1 DS tab BID × 3 days |
| Fosfomycin | 3 g × 1 dose |
| 2nd Line Treatment | |
| Fluoroquinolones:<br>Ciprofloxacin<br>Levofloxacin | <br>250 mg BID × 3 days<br>250 mg daily × 3 days |
| Beta Lactams:<br>Cefdinir<br>Cefaclor<br>Cefpodoxime proxetil | <br>100 mg BID × 5 days<br>250 mg TID × 5 days<br>100 mg BID × 3 days |
| *Uncomplicated cystitis is defined as occurring in a premenopausal, non- pregnant woman without structural or functional urinary tract abnormalities<br>**Not recommended if local resistance rates > 20% or if used in the previous 3 months | |

However, there are studies that suggest that up to 15-30% of patients with acute pyelonephritis are bacteremic.[47] For those patients who are considered to have complicated infections or are post-menopausal, blood cultures have proven beneficial.[48] Additionally, a large meta-analysis of studies on the utility of blood cultures concluded that they are beneficial in patients with sepsis.[49] Blood cultures are therefore recommended in patients with sepsis secondary to UTI.

**Radiologic Evaluation.** Imaging is typically unnecessary in cases of uncomplicated UTIs. If a patient with uncomplicated pyelonephritis has no resolution of symptoms after 72 hours of appropriate antimicrobial therapy, imaging may be warranted. In these patients, pre-contrast and post-contrast computed tomography (CT) of the abdomen and pelvis is the preferred method of imaging. Ultrasound and MRI may have a role in select patients, such as patients who have a contraindication or susceptibility to radiation or contrast. Conversely, the American College of Radiology recommends patients presenting with complicated UTI, especially those with urologic abnormalities or recent urologic surgery, have early imaging with pre- and post-contrast CT.[50]

**Ultrasound.** Ultrasound is non-invasive, does not involve radiation, is cost-effective, and can provide valuable clinical information at the bedside. Ultrasound can reveal complications such as hydronephrosis, renal or extrarenal abscesses, and distal hydroureter.[51-53] Bedside ultrasound for confirmation of nephrolithiasis is a quick and inexpensive tool for diagnosis, with sensitivity and specificity of 72-80% and 37-73%, respectively.[53,54] The American College of Radiology is of the opinion that ultrasound used in the evaluation of complicated UTIs provides only limited information and often does not identify a specific diagnosis.[55]

**CT Scan With and Without Contrast.** A non-contrast CT scan can accurately localize renal calculi, hydroureter, hydronephrosis, gas, and renal abscesses. The addition of contrast can better evaluate renal perfusion, and evaluate for renal artery occlusion, renal vein thrombosis, renal infarction, and abscess. The literature has shown that for the evaluation of flank pain, ultrasound has a sensitivity of 24%–77% compared to CT's sensitivity of 92%–96% for identifying the causative abnormality.[56-59] Given the increased sensitivity and ability to diagnose a

## Table 6. UTI Antibiotics Adverse Effects

| Medication | Common Adverse Effects* | Rare But Serious Adverse Effects |
|---|---|---|
| Nitrofurantoin | Nausea (8%)<br>Headache (6%)<br>Flatulence (1.5%) | Pulmonary hypersensitivity<br>Hepatotoxicity<br>Peripheral neuropathy<br>Hemolytic anemia (G-6PD)<br>*Clostridium difficile*-associated diarrhea (pseudomembranous colitis) |
| TMP-SMX | Nausea and vomiting<br>Anorexia<br>Allergic skin eruptions (rash, urticaria) | Stevens-Johnson syndrome and toxic epidermal necrolysis<br>Hepatic necrosis<br>Pulmonary hypersensitivity<br>*Clostridium difficile*-associated diarrhea (pseudomembranous colitis) |
| Fosfomycin | Diarrhea (10.4%)<br>Headache (10.3%)<br>Vaginitis (7.6%)<br>Nausea (5.2%)<br>Dizziness (2.3%),<br>Abdominal pain (2.2%)<br>Dyspepsia (1.8%),<br>Asthenia (1.7%) | *Clostridium difficile*-associated diarrhea (pseudomembranous colitis) |
| Ciprofloxacin | Nausea (2.5%)<br>Diarrhea (1.6%)<br>Vomiting (1%)<br>Rash (1%) | Tendinopathy and tendon rupture<br>Seizures and toxic psychosis<br>Hypersensitivity reactions<br>*Clostridium difficile*-associated diarrhea (pseudomembranous colitis)<br>QT interval prolongation |
| Levofloxacin | Nausea (7%)<br>Headache (6%)<br>Diarrhea (5%)<br>Insomnia (4%)<br>Constipation (3%)<br>Dizziness (3%)<br>Abdominal pain (2%)<br>Vomiting (2%)<br>Dyspepsia (2%)<br>Rash (2%) | Tendinopathy and tendon rupture<br>Seizures and toxic psychosis<br>Hypersensitivity reactions<br>*Clostridium difficile*-associated diarrhea (pseudomembranous colitis)<br>QT interval prolongation |
| Cefdinir | Diarrhea (15%)<br>Vaginal moniliasis (4%)<br>Nausea (3%)<br>Headache (2%)<br>Abdominal pain (1%)<br>Vaginitis (1%) | Beta-lactam allergic reactions<br>*Clostridium difficile*-associated diarrhea (pseudomembranous colitis) |
| Cefaclor | Diarrhea (3.4%)<br>Nausea (2.5%)<br>Vomiting and dyspepsia<br>Rash, urticaria, or pruritus (1.7%)<br>Vaginal moniliasis (2.5%)<br>Vaginitis (1.7%) | Beta-lactam allergic reactions<br>*Clostridium difficile*-associated diarrhea (pseudomembranous colitis)<br>Serum sickness reactions |
| Cefpodoxime proxetil | Diarrhea (7%)<br>Nausea (3.3%)<br>Vaginal infections (1.3%)<br>Abdominal pain (1.2%)<br>Headache (1%) | Beta-lactam allergic reactions<br>*Clostridium difficile*-associated diarrhea (pseudomembranous colitis) |

* Incidence taken from manufacturer prescribing information

## Table 7. Recommended Outpatient Antibiotics for Acute Uncomplicated Pyelonephritis[64]

| First-Line Treatment |
|---|
| Fluoroquinolones*:<br>Ciprofloxacin 500 mg BID × 7 days with/without initial 400 mg IV dose<br>Ciprofloxacin ER 1000 mg × 7 days<br>Levofloxacin 750 mg × 5 days |
| **Alternative Treatment for Patients Unable Take a Fluoroquinolone** |
| TMP-SMX 160/800 mg (double-strength tablet) BID × 14 days ** |
| Beta Lactam: Ceftriaxone 1 g IV or 24-hour consolidated dose of an aminoglycoside, followed by cefdinir, cefaclor, or cefpodoxime proxetil × 10-14 days** |
| *If local resistance rates > 10% a one-time dose of ceftriaxone or a 24-hour consolidated dose of an aminoglycoside should be given at the initiation of therapy.<br>**If susceptibility of the infecting organism is unknown a dose of ceftriaxone 1 g IV or a 24-hour consolidated IV dose of an aminoglycoside should be given at the initiation of therapy. |

multitude of pathology compared to ultrasound, a CT scan has proven to be the imaging modality of choice for renal pathology.[58,60-63]

## Differential Diagnosis

The differential diagnosis for UTI includes sexually transmitted infections (including herpes simplex, chlamydia, gonorrhea, and pelvic inflammatory disease), interstitial cystitis, urologic cancer, vaginitis, acute prostatitis, and epididymitis. Table 4 lists alternate diagnoses that should be contemplated when considering the diagnosis of UTI.

## Management

The results of urine culture are frequently not available at the initiation of treatment and, therefore, antibiotic selection for management of UTI is most often empiric. In recent years, development of antibiotic-resistant *E. coli* has altered antibiotic efficacy. Bacterial resistance patterns are geographically variable, so when available, local antibiograms should be referenced when choosing an antibiotic for treating UTI. Treatment of UTI is based on whether the lower or upper urinary tract is involved and on whether the infection is complicated or uncomplicated.

**Antibiotics for Patients with Uncomplicated Acute Cystitis.** For patients with uncomplicated acute cystitis, the IDSA recommends nitrofurantoin monohydrate/macrocrystals, trimethoprim-sulfamethoxazole (TMP-SMX), or fosfomycin as first-line management.[64] (*See Table 5.*)

Nitrofurantoin is highly effective for outpatient treatment of lower urinary tract infections, with less than 2% of *E. coli* being resistant.[65] The recommended dosing is 100 mg twice daily for 5 days. Nitrofurantoin is well tolerated, with nausea the most common side-effect. (*See Table 6.*) Because nitrofurantoin does not penetrate into the renal parenchyma, its use is limited to infections of the lower urinary tract, and it should not be used if pyelonephritis or renal abscess is suspected. Additionally, in the United States, nitrofurantoin is contraindicated in patients with a creatinine clearance less than 60, and therefore this agent may not be the best choice for patients with renal dysfunction or in elderly patients.

TMP-SMX 160/800 mg (1 double-strength tablet) twice daily for 3 days is also recommended as first-line empiric treatment for uncomplicated acute cystitis.[64] TMP-SMX has a low incidence of side-effects, but the sulfa component may cause a rash or adverse interaction with other medications. (*See Table 6.*) The North American Urinary Tract Infection Collaborative Alliance reported that *E. coli* isolates from outpatient specimens collected from 2003-2004 had approximately 21% resistance rate to TMP-SMX.[66] Therefore, local resistance rates should be reviewed before initiating therapy and, if resistance rates to TMP-SMX are in excess of 20%, another agent should be chosen for first-line empiric treatment.

There is minimal resistance to fosfomycin trometamol; however, it has a lower efficacy than the other short-course antibiotics.[64] One potential benefit of fosfomycin is that it is given as 3 g in a single dose. This makes fosfomycin an attractive choice for patients who are unable or unlikely to obtain prescription medications secondary to social or economic constraints. Diarrhea and headache are the most common side effects of fosfomycin. (*See Table 6.*) Like nitrofurantoin, fosfomycin does not achieve therapeutic renal tissue penetration and should not be used in cases of suspected early pyelonephritis.

Beta-lactam agents such as amoxicillin-clavulanate, cefdinir, cefaclor, cefpodoxime-proxetil, and cephalexin have lower efficacy than the first-line agents mentioned above and therefore are considered appropriate only as second-line agents for the empiric treatment of uncomplicated acute cystitis. Amoxicillin and ampicillin have high rates of resistance and are not recommended for empiric treatment in adults. Although highly effective for treatment of UTIs, a three-day course of a fluoroquinolone is not recommended as first-line treatment for uncomplicated cystitis so as to preserve efficacy for more complicated infections, infections of the upper urinary tract, and more acutely ill patients.[64]

**Antibiotics for Patients with Uncomplicated Pyelonephritis.** The 2010 IDSA guidelines for treatment of acute pyelonephritis can be categorized into outpatient versus inpatient management options. Table 7 summarizes the treatment recommendations for outpatients with acute uncomplicated pyelonephritis. Because pyelonephritis is a more severe infection than cystitis and because there can be significant complications from treatment failures in patients with pyelonephritis, the benefit of preserving the

fluoroquinolones to prevent the development of drug-resistant organisms does not outweigh the risk of treatment failure. Therefore, fluoroquinolones are considered the first-line antibiotic choice for uncomplicated pyelonephritis as long as the local resistance rates do not exceed 10%. Examples of acceptable dosing regimens include: ciprofloxacin 500 mg twice daily for 7 days, ciprofloxacin 1000 mg ER daily for 7 days, or levofloxacin 750 mg daily for 5 days. Resistance rates to fluoroquinolones in the United States remain low (approximately 3%) in patients with uncomplicated pyelonephritis.[66,67] However, if local antibiograms indicate an *E. coli* resistance rate to fluoroquinolones in excess of 10%, patients should be given a parenteral dose of a long-acting antimicrobial at the initiation of therapy and culture results should be followed for further changes in antibiotic management.[64]

TMP-SMX (1 DS twice daily for 14 days) is also an acceptable antibiotic for the management of acute uncomplicated pyelonephritis if the uropathogen susceptibility is known. *E. coli* resistance rates to TMP-SMX have been increasing; one multi-center study of emergency department patients presenting with pyelonephritis reported an *E. coli* resistance rate to TMP-SMX of approximately 20%.[67] Therefore, in cases of empiric treatment with TMP-SMX, a parenteral dose of a long-acting antimicrobial should be given at the initiation of therapy.[64] There is also increased risk of resistance to TMP-SMX with history of recent use, so if this history is elicited, it should prompt alternate antimicrobial selection.[67]

Beta-lactams for 10-14 days are less effective than fluoroquinolones, but could be considered as an alternative if use of a fluoroquinolone is prevented by patient allergy or a clinical contraindication. When beta-lactams are used for empiric treatment of uncomplicated pyelonephritis, an initial parenteral dose of a long-acting beta-lactam (e.g., ceftriaxone 1 g) is recommended.[64]

In patients requiring hospitalization for acute pyelonephritis, antibiotics should be administered via the parenteral route. Fluoroquinolones, an aminoglycoside +/- ampicillin, an extended spectrum cephalosporin, or penicillin +/- an aminoglycoside or IV carbapenam are all acceptable options.[64] The choice of antibiotic/s should be based on your hospital or local antibiogram.

**Antibiotics for Patients with Complicated UTI.** In comparison to uncomplicated UTI, the profile of infecting organisms in complicated UTI is expanded to include organisms typically found in healthcare-associated infections and immunocompromised individuals, such as Pseudomonas and fungi. Additionally, complicated UTIs are more often caused by organisms with antimicrobial resistance than uncomplicated UTIs are.[68] Therefore, guidelines for the treatment of complicated UTI are less clear than those for uncomplicated UTI and are often based on an assortment of variables, including medical comorbidities, severity of clinical presentation, recent antimicrobial exposure, previous culture results, and local/hospital resistance patterns. The fluoroquinolones are heavily studied in the treatment of complicated UTI; however, these studies are limited in the respect that they generally exclude patients with resistant organisms.[69] Bactrim has been shown to be inferior to fluoroquinolones for treatment of complicated UTI.[70] Typically oral antibiotics are appropriate, unless the severity of the clinical presentation dictates parental antibiotics.[69] Because of the prevalence of resistant bacterial species, urine culture results should be followed closely in these patients, and antibiotic management should be tailored to those results as soon as they become available. Specific management for select presentations of complicated UTI is further detailed in upcoming sections .

**Other Interventions.** In addition to antibiotics, antipyretics, antispasmodics, analgesics, antiemetics, and IV fluids may be appropriate for patients with urinary tract infections. The antispasmodic phenazopyridine is an azo dye that produces local analgesia of the bladder and urinary tract. When phenazopyridine is used in combination with an antibiotic in the first 48 hours after diagnosis of UTI, it has been shown to result in significant reduction of irritative voiding symptoms.[71]

## Special Populations

**UTI in Patients with Chronic Indwelling Catheters.** As previously stated, a catheter-associated UTI (CAUTI) refers to infection occurring in a person whose urinary tract is currently catheterized or has been catheterized within the previous 48 hours. CAUTI is defined as signs/symptoms of a urinary tract infection with a urine culture growing $10^3$ CFU/mL of one or more bacterial species in a catheterized urine specimen or in a midstream voided specimen. Although the absence of pyuria in a symptomatic patient with a urinary catheter is a strong indication that the symptoms are likely from an alternate diagnosis, the presence of pyuria alone is not diagnostic of a CAUTI.[72]

Management of CAUTIs starts with removal and replacement, if necessary, of the catheter. Urine cultures should be obtained either from the new catheter, prior to initiation of antibiotics, or if catheter replacement is unnecessary, from a midstream voided clean catch. Antimicrobials should be selected based on the patient's clinical status, local antibiograms, and patient's previous bacterial cultures and susceptibilities. The IDSA 2010 guidelines recommend seven days of antibiotics for patients with CAUTI who have prompt resolution of symptoms, and 10–14 days of antibiotics for patients with a delayed response. Alternatively, a five-day regimen of levofloxacin may be considered in patients with CAUTI who appear clinically well. A three-day antimicrobial regimen may be acceptable for women younger than 65 years old who develop CAUTI if the indwelling catheter has been removed.[72]

**Recurrent Uncomplicated UTI.** Recurrent UTI (rUTI) is defined as two uncomplicated infections in a six-month time period or three infections within a year.[73] The most common risk

factor for rUTI is increased frequency of sexual activity.[74] Treatment for initial recurrence in young, healthy women is the same as for other cases of uncomplicated UTI.[75] As the number and frequency of recurrences increases, the treatment strategy is less clear and suspicion for resistant bacterial infection increases.

**UTI in Pregnancy.** Several of the physiologic changes associated with pregnancy (ureteral dilation, urinary stasis, decreased bladder tone, and ureterovesical reflux) put pregnant women at increased risk for UTI. There are several differences in the way pregnant patients are managed, in comparison to the management of UTI in non-pregnant patients.

The first difference is that pregnant women, unlike other patients, should be treated for asymptomatic bacteriuria, defined as an asymptomatic patient with a catheterized urine specimen with one bacterial species isolated in a quantitative count ≥ $10^2$ CFU/mL.[16] The duration of antibiotic therapy for asymptomatic bacteriuria in pregnant women is 3-7 days.[16]

The second difference in the management of UTI in pregnant women is antibiotic selection. Care should be taken to avoid antibiotics that are teratogens or that may cause fetal harm. Nitrofurantoin is a pregnancy category B (caution advised, animal studies show no risk but human studies do not confirm) antibiotic, but has an increased risk of neonatal jaundice when used during the last 30 days prior to delivery.[76] There is conflicting evidence as to the safety of nitrofurantoin during the first trimester of pregnancy, with some studies reporting an increased risk of birth defects and others finding no difference.[76,77] Cephalosporins and fosfomycin are also pregnancy category B and generally considered safe in all trimesters of pregnancy. TMP-SMX is a folic acid antagonist and is therefore a pregnancy category D (weigh risk/benefit, positive evidence of human fetal risk) antibiotic. It has been associated with increased risk of cleft palate and cardiovascular defects when taken in the first trimester of pregnancy.[78] TMP-SMX has also traditionally been avoided in the third trimester of pregnancy because of a theoretical risk of hyperbilirubinemia and kernicterus in neonates. Recent literature has found no association between late-term use of TMP-SMX and kernicterus,[79] and therefore it is felt to be safe for use in both the second and third trimesters of pregnancy.[80] The fluoroquinolones are a pregnancy category C (weigh risk/benefit, animal studies show adverse fetal effects, but no controlled human studies) and have traditionally been avoided in pregnancy; however, there is recent literature to suggest that fluoroquinolone use may be safe in pregnancy.[77,81] Further study is likely needed in this area before changing clinical practice. The optimal duration of antimicrobial therapy for the pregnant patient with cystitis is not well defined, but typically longer courses of antibiotics are recommended so as to avoid recurrence of infection or treatment failure.

The third major difference in managing the pregnant patient with UTI is in disposition planning for the patient. It is classically taught that all pregnant patients with pyelonephritis require hospitalization. While the threshold for hospitalizing pregnant patients with pyelonephritis is lower than for the general population, there is evidence to suggest that outpatient management with two doses of IM ceftriaxone, followed by a 10-day course of oral cephalexin may be appropriate for select individuals.[82,83] Due to the need for close follow-up and repeat evaluation, outpatient management of pregnant patients with pyelonephritis should be done in close consultation with the physician managing the patient's pregnancy. Appropriate antibiotic regimens for hospitalized pregnant patients with pyelonephritis include IM ceftriaxone, IV cefazolin, or IV gentamicin plus ampicillin.[84]

**UTI Associated with Urinary Stones.** UTIs associated with urinary stones appear to have a different profile of bacterial predominance than uncomplicated UTIs. Proteus and Pseudomonas species appear to be more prevalent, while *E. coli* and Enterococcus are less frequent than in patients without stones.[85] Successful treatment of UTI in these patients requires complete removal of the stone in combination with antimicrobial therapy. In patients with non-obstructive stones, it may be reasonable to allow for the stone to pass without intervention; however, in patients with obstructive ureterolithiasis, emergency consultation with urology is recommended.

**Sepsis Secondary to UTI.** Early identification and prompt treatment of patients at risk for sepsis secondary to UTI is essential for improving morbidity and mortality. When a UTI is diagnosed in a patient with systemic inflammatory response syndrome (SIRS) [defined by the presence of ≥ 2 of the following criteria: temperature < 36˚C or > 38˚C, heart rate > 90 beats/minute, respiratory rate > 20 breaths/minute or partial pressure of carbon dioxide of < 32 mmHg, white blood cell count < 4000 cells/$mm^3$ or > 12,000 cells/$mm^3$ or > 10% immature neutrophils (bands)],[86] the patient is considered to have sepsis secondary to UTI. These patients are at increased risk for severe sepsis and septic shock, and early aggressive treatment is recommended. Severe sepsis is defined as sepsis with organ dysfunction, hypotension, and/or signs of tissue hypoperfusion (elevated lactate). Septic shock is defined as sepsis with persistent hypotension despite the administration of IV fluids.

Initial management of patients with sepsis secondary to UTI should include immediate removal of any pre-existing urinary catheter with replacement if necessary. Broad-spectrum antibiotics should rapidly be administered, preferably after blood and urine cultures have been collected. If the patient has undergone a recent urologic procedure or had a urinary catheter, consideration should be given to nosocomial infections, such as *Pseudomonas aeruginosa*, and multi-drug-resistant organisms, such as Enterobacteriaceae with extended spectrum beta-lactamases.[87]

IV fluids should be used aggressively

and vasopressors should be initiated for continued hypotension despite adequate volume resuscitation.

Obstruction of the upper urinary tract is a common cause of sepsis secondary to UTI. In the setting of urosepsis, the causative urological obstruction requiring intervention, such as obstructive ureterolithiasis or ureteral stenosis, should be intervened upon, preferably within six hours of presentation.[87]

## Disposition

In general, patients with acute uncomplicated UTI can be treated as outpatients. Admission should be considered for patients who are unable to tolerate oral antibiotics, have pain that is uncontrolled with oral analgesics, have immune compromise, have UTI complicated by obstruction or renal abscess, have a barrier to obtaining appropriate follow-up or prescribed antibiotics, appear clinically ill, or meet sepsis, severe sepsis, or septic shock criteria. As mentioned previously, pregnant patients with cystitis can generally be managed as outpatients, as long as above criteria are met. Pregnant patients with pyelonephritis may selectively be managed as outpatients if they have close follow-up with their prenatal care provider and can obtain repeated dosing of IM ceftriaxone 24 hours after emergency department discharge.

## Summary

Urinary tract infections are common infections in young, healthy women and account for a large number of visits to ambulatory centers, including emergency departments. Uncomplicated UTIs generally have a straightforward presentation with fairly typical symptoms, and in many cases can be managed without the utilization of any diagnostic studies. When the diagnosis is not clear, the urine dipstick and urine microanalysis can aid in diagnosis. Although urine culture is unnecessary in cases of uncomplicated UTI, it can be useful in modifying antimicrobial treatment for complicated infections. The IDSA has published recommendations to guide antibiotic selection; however, local antibiograms should also be utilized in choosing specific antibiotics for your patient. Severe sepsis and septic shock are highly morbid complications of UTI, and patients at risk for sepsis syndrome or those already presenting with sepsis syndrome should be managed aggressively with early antibiotics and IV fluids. Special considerations should be given to patients with nephrolithiasis, indwelling urinary catheters, and to patients who are pregnant.

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## CME Questions

1. What is the most common causative agent of both complicated and uncomplicated UTI?
   A. *Staphylococcus saprophyticus*
   B. *E. coli*
   C. Pseudomonas
   D. Enterobacter
   E. Klebsiella
2. The dominant risk factor for a diabetic having a UTI is:
   A. uncontrolled glucose
   B. history of neuropathy
   C. age
   D. hemoglobin A1C
   E. type of glycemic therapy
3. The leading risk factor for catheter-associated UTI is:
   A. diabetes mellitus
   B. serum creatinine > 2
   C. placement outside of the operating room
   D. duration of the catheter
   E. age < 55 years
4. According to IDSA guidelines, when do you send a urine culture?
   A. for pyelonephritis
   B. for pregnant females
   C. for admitted patients
   D. for every urinary tract infection
5. What is the imaging modality of choice for renal pathology?
   A. ultrasound
   B. IVU
   C. CT scan
   D. X-ray
6. What is the most specific finding on urine dipstick for UTI?
   A. leukocyte esterase
   B. nitrites
   C. blood
   D. protein
7. According to IDSA 2010 guidelines, all of the following would be appropriate for empiric treatment of uncomplicated acute cystitis, *except*:
   A. TMP-SMX
   B. ampicillin
   C. fosfomycin
   D. nitrofurantoin
8. Which of the following antibiotics is most appropriate for outpatient treatment of acute uncomplicated pyelonephritis?
   A. nitrofurantoin
   B. fosfomycin
   C. amoxicillin
   D. ciprofloxacin
9. Which physiologic change(s) puts pregnant women at increased risk for UTI?
   A. ureteral dilation
   B. urinary stasis
   C. decreased bladder tone
   D. ureterovesical reflux
   E. all of the above


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